

Perspective

DPP-4 inhibitors and angioedema: a cause for concern?

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INTRODUCTION

Medications are frequently associated with angioedema, a leading cause of hospitalizations for hypersensitivity reactions in the United States.¹ Antihypertensives, likely angiotensin-converting enzyme inhibitors (ACEI), are the most commonly identified class, accounting for approximately 1 in 4 of these hospitalizations.¹ A progressive rise has been noted in the prevalence of ACEI-associated angioedema, which is most likely a consequence of increased utilization. Dipeptidyl peptidase IV inhibitors (DPP-4I) are often used concurrently with ACEI, and this combination may increase the potential for development of angioedema.

A new class of medications, the DPP-4I, was introduced to the United States market in 2006 for the management of type 2 diabetes. This class has interesting physiologic effects and mechanisms that also may increase the possibility of hypersensitivity reactions. Sitagliptin (Januvia) was the first medication approved, followed in 2009 by saxagliptin (Onglyza). In 2007, postmarketing reports of hypersensitivity reactions with sitagliptin, including angioedema, prompted warnings and labeling changes.² The labeling for saxagliptin also reports hypersensitivity reactions that occurred in pre-approval clinical trials.³

The most recent treatment algorithm published by the American College of Endocrinology promotes the use of DPP-4I as a first-line option for management of type 2 diabetes mellitus (DM).⁴ This recommendation will likely result in increased utilization of this class of medications, which may potentially lead to increased reports of hypersensitivity reactions. With hypertension (HTN) as a common comorbidity of DM, many patients will likely be managed with both ACEI and DPP-4I. Thus, in DM patients with HTN who develop angioedema, there may be significant potential

for incorrectly attributing the reaction solely to ACEI or angiotensin receptor blocker (ARB) therapy. Currently, few data are available to confirm the clinical impact and associations of DPP-4I and angioedema, including any additive or synergistic angioedema risk in patients taking both ACEI/ARB and DPP-4I.

CLINICAL REPORTS AND CORRELATES OF ANGIOEDEMA WITH DPP-4 INHIBITORS

Limited data from voluntary reports link angioedema with DPP-4I through the Adverse Events Reporting System. There is, however, one report in the literature of a patient being discontinued from a study of sitagliptin because of a hospitalization for angioedema.⁵

A recent meta-analysis analyzed multiple studies reporting that DPP-4I affect the risk for clinical angioedema. Using clinical trials data ($n = 13,921$) for patients taking vildagliptin (another DPP-4I) approved in Europe, 19 cases of angioedema were confirmed, with 9 additional cases having insufficient evidence to verify association with vildagliptin therapy. Most patients exhibiting angioedema (73%) were also taking an ACEI at the time of diagnosis. No significant differences in angioedema rates were found between patients taking vildagliptin compared with either placebo or another oral hypoglycemic agent. No racial differences in the incidence of angioedema and no deaths or intubations were noted as a result of the reaction. However, patients taking both an ACEI and vildagliptin had an increased overall angioedema rate of 0.51% (OR 9.29; CI 1.22–70.70, $P < .05$), with a higher rate of 0.58% (OR 10.59; CI 1.24–90.81, $P < .05$) in those taking the maximum daily recommended dose of vildagliptin—100 mg. In all cases, vildagliptin was initiated after the ACEI. Vildagliptin-treated patients who were not taking an ACEI had no increased risk of angioedema, regardless of its dose.⁶

In this same review, the authors also retrospectively examined reports of hypersensitivity reactions from Food and Drug Administration postmarketing data for sitagliptin, along with published clinical trials on sitagliptin, saxagliptin, and alogliptin (another DPP-4I in development).⁶ Fourteen postmarketing cases of sitagliptin-associated angioedema were reviewed. Information about concurrent medications was not available. Sitagliptin was associated with more severe reac-

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tions in comparison with vildagliptin, including 5 hospitalizations and 3 intensive care admissions, one of which required intubation of the patient.⁶ The manufacturers of both vildagliptin and alogliptin have subsequently withdrawn their United States new drug applications. A recent review of Food and Drug Administration–reported postmarketing adverse events for sitagliptin found only 4 cases of angioedema. However, in contrast to other reports, this review modified case definitions to exclude anyone with airway obstruction or airway “symptomatology.” The authors proposed that an altered immune function status could be the underlying mechanism for angioedema and other hypersensitivity reactions to sitagliptin.⁷

More recent evidence raises other questions regarding the combined use of DPP-4I and ACEI. An interactive hemodynamic effect occurs with combined therapy, and, depending on the extent of ACE inhibition, blood pressure may actually be increased. Sympathetic nervous system activation by DPP-4I was observed in patients taking normal doses of ACEI.⁸

Angiotensin receptor blockers are also associated with angioedema, though the risk is much lower than with ACEI, and the pathway is unknown.⁹ One case of angioedema has been reported with the concurrent use of an ARB and a DPP-4I; the patient was taking the ARB for an unknown length of time and did not experience angioedema until after the initiation and subsequent rechallenge with sitagliptin.¹⁰ This case report suggests that DPP-4I should not be ruled out as an underlying cause or contributing factor for the development of angioedema, especially in patients taking concurrent ACEI or ARB.

DPP-4 INHIBITORS AND MECHANISMS OF ANGIOEDEMA

In patients with type 2 DM, DPP-4I act by preventing metabolism of the incretin hormones, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, thus leading to increased total body levels. Physiological levels of these hormones normally increase in response to food and help regulate glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion. In addition to these hormone effects, DPP-4 plays a secondary role in the substance P (sP) and bradykinin (BK) metabolic pathways.^{11–13}

One commonly proposed mechanism for the development of angioedema from DPP-4I and ACEI use involves the generation of BK.^{11–13} Angiotensin-converting enzyme is a major component of the primary degradation pathway for BK and sP. The DPP-4 functions as a secondary metabolic pathway. When ACE activity is decreased (as with the use of ACEI), secondary pathways including DPP-4 attain a more substantial role for metabolism of sP and BK.¹³ Both molecules increase vascular permeability, and, in animal studies, high levels of both have been associated with tracheal edema.¹⁴ In humans, previous studies have indicated that normal degradation pathways of these substrates may be

impaired in patients who have demonstrated ACEI-associated angioedema.^{11,15}

In one study, patients presenting with ACEI-associated angioedema were found to have decreased serum DPP-4 activity during the initial but not the later phases of angioedema. In this brief study, the patients studied included 1 with rheumatoid arthritis on immunosuppressive therapy, 2 with heart transplants, and 1 with a history of malignancy.¹⁵ Autoimmune diseases and metastatic malignancy have been associated with angioedema, perhaps from reduced DPP-4 enzyme activity versus C1 esterase inhibitor deficiency.¹⁶ Immunosuppressive drugs, specifically mammalian target of rapamycin inhibitors (such as rapamycin or sirolimus), are also reported to cause angioedema, either alone or in combination with ACEI.¹⁷

In another case-control study, DPP-4 activity and serum protein levels were both found to be decreased in individuals with ACEI-associated angioedema compared with ACEI-exposed control subjects without angioedema. Those currently taking an ACEI also demonstrated an inverse correlation between DPP-4 protein and prolonged ex vivo half-life of sP, suggesting that the relative contribution of DPP-4 to sP degradation is increased in the setting of ACE inhibition.¹¹ In addition, the findings of this study suggest that individuals concurrently treated with an ACEI and DPP-4I may be at increased risk for the development of angioedema. Conclusions from the studies reviewed suggest that defects in DPP-4 activity may be acquired and predispose particular patients to ACEI-associated angioedema, or, alternatively, genetic factors may modulate the effect of environmental factors on DPP-4 activity.^{11,15}

Conversely, chronic hyperglycemia theoretically may have an intrinsic protective mechanism against the development of angioedema in patients with type 2 DM. The DPP-4 activity is often elevated in patients with uncontrolled type 2 DM. These elevations in activity were not found in patients with type 1 DM or in those newly diagnosed with type 2 DM and hemoglobin A1c less than 7.5%.¹⁸ The clinical implications of this are unknown but may become clearer if a relationship between poorly controlled type 2 DM and increased incidence of angioedema can be established.

DISCUSSION

Most health care providers are aware of the risk for ACEI and ARB-associated angioedema, which can at times be life-threatening. Accordingly, patients being evaluated for new-onset angioedema are queried about the use of ACEI or ARB, and, if associated with an episode of angioedema, are discontinued for life from this drug category. This is not a trivial decision, because ACEI/ARB have become first-line therapy for hypertension in many clinical settings. Because of limited use and relative sparse data, the incidence and prevalence of DPP-4I-associated angioedema remain unclear. Health care providers should be aware that angioedema has been associated with DPP-4I, either alone or when used concomitantly with certain classes of medications, including ACEI/ARB.

The therapeutic role of DPP-4I in patients with DM continues to develop. Considering the common occurrence of HTN in DM patients and the broad use of ACEI for HTN, health care providers and patients should be aware of a theoretical increased risk of angioedema when these medications are combined. Additionally, health care providers should be judicious when prescribing DPP-4 inhibitors in patients with a history of angioedema. Further work is needed in establishing the true risks for these medications—alone or in combination—for specific patient populations.

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